

January 2017

Study Title: Dot Efficacy Study Effectiveness of a Personalized Approach for Pregnancy
Prevention: Dynamic Optimal Timing

Clinical Trials Number: **NCT02833922**

* Please enter the title of your study:

1Dot Efficacy Study

. Effectiveness of a Personalized Approach for Pregnancy Prevention: Dynamic Optimal Timing

Below is a system generated "short title". It will only be used to reference the protocol in the system. All official letters and minutes will include the long title entered above.

Dot Efficacy Study Effectiveness of a Personalized Approach for Pregnancy Prevention:
Dynamic Optimal Timing (original version)

2* Please specify the Principal Investigator:

. [Victoria Jennings](#)

If the Responsible Participant is somebody other than the Principal Investigator, please specify that individual here:

Investigator(s): Any person who is responsible for the design, conduct or reporting of research.

3 **Engaged Study Team Members:** An individual is "engaged" in human subjects research when the individual, (i) intervenes or interacts with living individuals for research purposes; or (ii) obtains individually identifiable private information for research purposes [45 CFR 46.102(d),(f)].

Please note: All members of the study team that are "engaged in research" (i.e. investigators, co-investigators, consultants, etc.) or who appear on the grant will be required to submit a Study Specific Disclosure Form at the time of initial and continuing review for this study.
Please specify the Co-Investigators:

4 Name	Department	E-Mail
. Rebecca Simmons	Institute For Reproductive Health (IRH)	rebecca.simmons@georgetown.edu
Dominick Shattuck	Institute For Reproductive Health (IRH)	ds1380@georgetown.edu

5 Please specify the Regulatory Coordinator(s)

Name	Department	E-Mail
There are no items to display		

Please specify the Study Coordinator(s):

6

Name	Department	E-Mail
. Elizabeth Menstell	Institute For Reproductive Health (IRH)	ecm104@georgetown.edu

7Please specify the Research Nurse(s):

.

There are no items to display
Please specify the Biostatician(s):

1.1 - Training Certification Summary:

Note: The dates in this section are intentionally blank as we move toward digitizing the IRB training records. In the future the fields will be populated with real data.

Training Certifications for all Study Team Members engaged in research

Person

1. [Rebecca Simmons](#)
[Dominick Shattuck](#)
[Elizabeth Menstell](#)
[Victoria Jennings](#)

Training Certifications for additional team members listed on grant:

2. Last Name First Name Dept. Title Certification Date IRB Renewal Deadline
There are no items to display

1.3 - Is the Study Human Subject Research?

* Is the activity a systematic investigation designed to develop or contribute to generalizable knowledge? In other words, do you intend to publish or

1. otherwise share the results outside the institution?

☒ Yes ☐ No

* Does the research involve obtaining information about living individuals?

2. ☒ Yes ☐ No

* Does the research involve intervention or interaction with the individuals?

3. ☒ Yes ☐ No

Is this activity an **individual use** of a Humanitarian Use Device (HUD)?

4. ☐ Yes ☒ No

[Help](#)
[Information on](#)
[HUD](#)

1.5 - Type of Review

Please select the review type that you are seeking.

If you believe that your research is eligible for either Expedited or Exempt Review, you may select it below. Otherwise you should apply for Full Board Review.

Expedited Review

Research activities that (1) present no more than minimal risk to human subjects and (2) involve only procedures listed in one or more of the categories ([link](#)) may be reviewed by the IRB through the expedited review procedure. Minimal risk means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Exempt Review

Some research involving human subjects may be exempt from IRB review. The categories ([link](#)) describe these exemptions. Please note that an exemption can be invoked only if all components

of the research fit the category as described. You might find the following decision charts helpful: <http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html>

Full Board Review

All research that does not meet the criteria listed above should apply for Full Board Review.

* Please select the review type you are seeking:

- ☐ Exempt Review
- ☐ Expedited Review
- 1. ☒ Full Board Review
- ☐ Facilitated (NCI CIRB or IRB of Record)
- ☐ Facilitated: Commercial IRB (IRB of Record)

2.0 - Type of Research

* Please select the research type that best describes the current study

- ☐ Biomedical
- 1. ☐ Oncology
- ☒ Social/Behavioral

2.0.1 - Status of Research

* What is the status of your research?

1. Other

"Other" should be selected if:

- No participants have been enrolled to date
- Recruitment and/or enrollment of new participants or review of records/specimens continue; OR

- The study is no longer actively enrolling, but subjects are still involved in research-related activities. (e.g., still receiving treatment, obtaining blood draws)

"Long Term Followup" should be selected when the study is no longer enrolling and participants have completed research-related activities. The study remains active **only** for long-term follow-up.

"Data Analysis" is intended for studies where study enrollment is permanently closed, all participants have completed all research-related activities, and long-term followup has been completed. All data collection is complete and the remaining research activities are related to data analysis only.

2.1 - GHUCCTS

* Is this study a GHUCCTS study?

☐ ☐ Yes ☒ ☒ **No**

1.

[GHUCCTS is the Georgetown-Howard Universities Center for Clinical and Translational Science.](#)

2.3 - Thesis or Dissertation

* Is this research done for your thesis/dissertation?

1. ☐ ☐ Yes ☒ ☒ **No**

2.7 - NCI Central IRB

* Are you using the NCI Central IRB

1. (NCI-CIRB) for this study?

☐ ☐ Yes ☒ ☒ **No**

NCI is the National Cancer Institute at the National Institutes of Health (NIH)

2.9 - Collaboration With Another Institution

* Are you collaborating with another institution for this study?

1. ☒ ☒ **Yes** ☐ ☐ **No**

2.10 - IRB of Record

* Is the Georgetown University IRB the IRB of Record for the study?

1. ☒ ☒ **Yes** ☐ ☐ **No**

Note: It is the responsibility of the Georgetown University PI to ensure that all collaborating sites have obtained IRB approval and that procedures are in place to ensure that approved protocol, informed consent documents, and adverse event reports are disseminated to all participating sites. You must also complete a "Determination/Notification IRB of Record for Human Subject Research Projects" form, which can be found on the IRB's website at <http://ora.georgetown.edu/irb>.

Please inform the investigators from the collaborating sites that their local IRB should contact the Georgetown University IRB directly to discuss institutional agreements.

3.0 - Funding

* Is the project being sponsored or funded by GHUCCTS?

1. ☐ ☐ Yes ☒ ☒ **No**

*

Does the project utilize GHUCCTS services or facilities?
(for example study is conducted on the Clinical Research Unit

2. (CRU) <http://cru.gumc.georgetown.edu/>)

☐ ☐ Yes ☒ ☒ **No**

* Please select the source(s) of funding for your project:

- ☐ No Funding
- ☐ PI's internal department funds and/or unrestricted
- ☐ University (discretionary) funds
- ☐ Industry/Commercial Sponsor
- ☐ Cooperative Group
- 3. ☒ Federal, non-NIH
- ☒ Federal, NIH
- ☐ Local/State Government
- ☐ Foundation/Non-Profit

- ☐ Other external support (for example, PI initiated or other)

3.6 - Funding - Federal Non-NIH

You selected:

Federal Non-NIH funding.

- * Please select the funding mechanism:
1. Other
 2. If you selected "Other", please specify:
United States Agency for International Development
 3. * Has the grant been awarded, or is the award pending?
Awarded
 4. * Is Georgetown University (GU) the primary awardee institution?
GU is the primary awardee institution

3.11 - Funding - Grant and PI Information

You selected:

GU is the primary awardee institution

- * Is the PI on the grant the same as the PI of the study?
1. ☒ ☒ **Yes** ☐ ☐ **No**
 2. * Is the title of the grant the same as the title of this human subject research application?
☐ ☐ **Yes** ☒ ☒ **No**
 3. * Please provide the identifying grant number:
GR409775
- * Please attach a copy of the entire grant proposal (excluding appendices) **AND** the Grants & Contracts Transmittal Form submitted to the Office of Sponsored Research, if available. **Please remove salary information, SSNs, and DOBs.**

Name	Version
FACT Project budget TRACS (2).pdf History	0.01
FACT Project fully executed mod (2).pdf History	0.01
Georgetown University - FACT Cooperative Agreement fully executed (2).pdf History	0.01
IRH Budget Justification FINAL.docx History	0.01
IRH USAID - 5 yr Breakdown Budget 6-12-13 FINAL. (3).pdf History	0.01

Note: The IRB is required by the Federal Office of Human Research Protection (OHRP) to review the grant proposal and human research application for consistency. You may be asked to explain discrepancies, if any, identified by the IRB during the review process.

See <http://www.hhs.gov/ohrp/humansubjects/guidance/aplrev.htm> for more information about IRB responsibilities regarding grant review.

3.13 - Funding - Grant Title Detail

You indicated that the title of the grant is different from the title of this human subject research application.

- * Please specify the title of the grant:
1. FACT: Fertility Awareness for Community Transformations Project

4.0 - Conflict of Interest

Each “investigator” must submit a Georgetown University Study Specific Disclosure Form (SSDF) as part of this protocol application. “Investigator” includes the principal investigator and any other person who is responsible for the design, conduct, or reporting of research.

The SSDF can be submitted from the study workspace. Financial interests related to the research must be disclosed in the consent form; you will receive guidance on what needs to be disclosed and how you should proceed from the Office of Regulatory Affairs via the IRB office. The institution will also determine if a conflict management plan is appropriate to address an investigator's related financial interests.

Questions about the Georgetown University Study Specific Disclosure Form can be directed to the Office of Regulatory Affairs at (202) 687-3354 or amc461@georgetown.edu.

Guidance for Conflicts Disclosure in Publications and Presentations

Financial and/or Intellectual property interests (e.g. patents or patent applications) must be disclosed in all related consent forms, press releases, publications, and presentations.

6.15 - Data Repositories

* Does this study include a data repository?

☒ ☒ **Yes** ☐ ☐ **No**

1. *Note: The collection and storage of specimens/data becomes a research repository when there is a specific intention for the data/specimens to be used repeatedly for research purposes, or stored for future research and/or shared with other investigators.*

If you answered yes to #1, are family members being asked to provide data?

2. ☐ ☐ **Yes** ☒ ☒ **No**

If you answered yes to #1, please specify what resources are needed to maintain this data repository:

3. Ensuring the security and confidentiality of the research data collect is paramount. Research data entered into the DOT app will be transmitted and stored in an encrypted fashion and be inaccessible to outside networks. Once data is entered into the DOT application, it will be transmitted over a Transport Layer Security (TLS) encrypted connection to the projects

Research Web Portal application.

The Research Web Portal consists of a web application and database. The web application will be the user facing interface for research participants, call center staff and IRH research staff. Each will have a separate and role specific interface. Research participants will have access to study and general health information. Call center staff will be able to interact with research participants on an as needed basis. Call center staff will have read only access to specific and limited participant data in order to carry out elements of the research protocol. Authorized IRH research staff will be able to view built-in reports and pull down data sets as necessary. The research database will be setup on a separate dedicated server and isolated from the public Internet. Data stored on in the research database will be encrypted at the cell level. Direct access to the research database will be restricted to authorized IRH and HITLAB staff. Access to the Research Web Portal and DOT application transactions will be logged and monitored for unusual activity, unauthorized access attempts and to support compliance requirements (e.g. HIPAA).

All data security measures will be pre-tested prior to implementation, both to ensure feasibility and to test security features.

10.0 - Information for Protocol Review - Study Description

Please summarize the protocol according to the following:

* Purpose of project (one or two sentences):

1. The purpose of this study is to determine the efficacy and effectiveness of the mobile app Dot. The use of mobile phones for family planning is novel, and women's ability to understand and use the app is unknown. Thus, the study will also explore usability and assess acceptability of a mobile phone app to support use of this family planning method based on fertility awareness.

* Which methods will this study include?

2. Qualitative Social Science

Survey Research

* Study design (for example, hypothesis, research questions, standard and experimental procedures/drugs/devices or equipment, etc.):

The primary objective of this study is to determine the efficacy/effectiveness of the DOT algorithm under two conditions: 1) correct (or perfect) use, when a woman does not have unprotected intercourse on days identified as fertile; and 2) typical use, when a woman has occasional unprotected intercourse on days identified as fertile. We hypothesize that:

3. Hypothesis 1: For correct use DOT will have a failure rate <3 (no more than 3 pregnancies per 100 woman years of correct use), and;
Hypothesis 2: For typical use DOT will have a failure rate <12 (no more than 12 pregnancies per 100 woman years of typical use)

Hypothesis 1 is based on calculations described in the following abstract submitted for publication: Personalized Estimation of a Woman's Most Fertile Days
Li, Heyer, Jennings, Smith, & Dunson

Abstract

Objective: To propose a new personalized approach of estimating a woman's most fertile days that only requires recording the first day of menses and can leverage the capabilities of smartphone applications to convey this information to a user so she can plan or prevent pregnancy.

Methods: We performed a retrospective analysis of two prospective cohort studies (one North Carolina based Study and the Early Pregnancy Study [EPS]) and a prospective multicenter trial (World Health Organization [WHO] study). One North Carolina study consisted of 68 sexually active women with either an intrauterine device or tubal ligation. The second North Carolina study comprised 221 women who planned to become pregnant by discontinuing any use of birth control and had no known fertility problems. The WHO study consisted of 706 women from five geographically and culturally diverse settings. Bayesian statistical methods were used to design our proposed method (DOT), and simulation studies were used to estimate the cumulative pregnancy risk.

Results: For one method of flagging days, simulation analyses indicate a 4.4% cumulative probability of pregnancy over 13 cycles with correct use. After a calibration window, this method flags between 11 and 13 days where unprotected intercourse should be avoided per cycle. Eligible women should have cycle lengths between 20-40 days and a range less than or equal to 9 days.

Conclusions: DOT can be easily implemented by computer or smart phone apps, allowing for women to make more informed decisions about their fertility. This approach is already incorporated into a patent-pending system and is available for free download on iPhones and Androids.)

Hypothesis 2 is based on previous studies calculated by IRH on a similar method of family planning, the Standard Days

Method (Arevalo, Jennigs, & Sainai, 2002, Efficacy of a new method of family planning: the Standard Days Method)

Research Questions

The research questions associated with each study objective are described below.

Objectives Research Questions

Primary objective: To determine the efficacy/effectiveness of the DOT algorithm under correct use.

- What is the efficacy/failure rate of DOT when used correctly (no unprotected intercourse on days identified as fertile)?
- What is the difference in efficacy/failure rate of DOT with no reported intercourse on days identified as fertile compared to protected intercourse on those days?
- On what days of their cycle (with what percentage risk as calculated by DOT) did women who became pregnant report having intercourse?

Primary objective: To determine the efficacy/effectiveness of the DOT algorithm under typical use.

- What is the effectiveness/failure rate of DOT with typical use (unprotected intercourse on

days identified as fertile, misunderstanding of fertile days or disregarding risk)?

Secondary objective: Describe the profile of DOT users.

- What are the demographic characteristics of DOT users (age, parity, marital status, etc.)?
- What method(s) were they using prior to choosing DOT (ever, immediately before)?
- How do women find out about Dot?
- Why do they choose to use it?
- What percent of women use Dot correctly in all of their cycles (correctly understand app information about fertile days, avoid unprotected intercourse on all fertile days)?

Secondary objective: Describe how DOT is being used.

- In what percent of cycles is DOT used correctly?
- In what percent of cycles is there no reported intercourse on fertile days?
- When are users engaging in unprotected intercourse on fertile days? (i.e., are they more likely to do this in the first few cycles when the window is longer and/or before they become accustomed to it?)
- In what percent of cycles, and on what percent of days, is there condom use on fertile days? EC use?
- What strategies do women use to avoid having unprotected intercourse on fertile days?
- What percentage of women chose to IGNORE a cycle? If so, why did they IGNORE it? (Note: Dot has an “ignore” option for women who have a cycle that is “unusual” for them. It allows the woman to tell Dot to ignore that cycle for purposes of calculating her fertile days. The explanation is that something unusual happened during that cycle, such as EC use, a pregnancy loss, serious illness, etc.) Note, that IGNORED cycles are still included in efficacy/effectiveness calculations.

Secondary objective: Understand reasons for discontinuation of DOT.

- Why do women stop using DOT for pregnancy prevention?
- What do women who stop using DOT and want to avoid pregnancy do to prevent pregnancy?
- What is the profile of women who discontinue use of the method?

Secondary objective: Determine user understanding of DOT messages.

- Do women generally understand the messaging that appears on the Dot app about high and low risk?
- Do they understand messaging about when their next period is likely to start?
- If it is determined that a woman is not a good candidate for using DOT (she has cycles shorter than 20 days, longer than 40 days or highly variable), does she understand that she should not use DOT for pregnancy prevention?

Secondary objective: Describe user feedback on using DOT interface and method.

- How can DOT be improved (e.g., identified fertile time reduced, efficacy increased)?
- Do women experience any technical problems in using Dot? What are the problems?
- What specific pages do women most utilize (e.g., profile page, FAQ's, other) within the app? What information do they report is most helpful?

Study related data will come from four sources:

- Information provided through women's interaction with and regular use of the app
 - Period start date
 - How each day is flagged in terms of probability of pregnancy (high/low)
 - Distribution of daily probability of pregnancy
- Information entered by an individual woman via the research module of the app
 - Daily intercourse information, protected/unprotected
 - Period start dates
 - Responses to periodic questions/self-administered questionnaires transmitted by the app
- Information provided by women during interviews (with an interviewer trained by IRH and based in a carefully-selected health-focused call center), consisting of
 - Verbal consent obtained and noted in participant file
 - Enrollment interview (responses to screening questions, additional demographic data)
 - Phone interview following the first cycle of study participation (confirming continued intent to avoid pregnancy and to use Dot, perceptions of Dot)
 - Exit interview (assessing reason for exit, e.g., completed study, pregnancy, not eligible to use DOT, preference for another method)
- Pregnancy information (women who state that they are- or believe that they are- pregnant during the study will be sent a pregnancy test kit and asked to provide a photo of a positive or negative pregnancy test result)

We will use a prospective, non-randomized, non-controlled design to test the efficacy/effectiveness of DOT among culturally diverse populations in the United States, with the intention of utilizing study findings to assess the introduction, use, and effect of Dot in a variety of additional countries, pending study findings. We proposed this approach because there is no app currently available to which Dot can reasonably be compared. Women using the CycleBeads app, for example, should meet certain cycle length and variability criteria, a limitation Dot is designed to address. Women who use apps requiring daily checking of temperatures and/or cervical secretions have opted to use an approach that is considerably more complex and requires much more monitoring than Dot. Therefore, a comparative study is not feasible.

In designing this study, we followed the guidelines recommended by Trussell and Kost (1987). Data collection, participant enrollment, and pregnancy definition are all influenced by their recommendations. Their guidelines also affect the way we will analyze the data. We will apply this approach by 1) assessing both perfect and typical use, 2) using life-table analysis (in addition to establishing a Pearl index), and 3) observing women for up to 13 cycles of use. The approach will need to be adapted to meet the requirements of an app-based fertility awareness method. As there is virtually no experience conducting an app-based efficacy study for a method women access on their own prior to being recruited for the study, we will 4) attempt to minimize loss to follow-up by engaging women over time via the app and through communication with a call center. We will 5) count pregnancies as reported by the woman, inquiring about her pregnancy status as soon as she fails to enter her period start date at the expected time to minimize undercounting pregnancies. Pregnancy results will be reported via a photo of a completed home pregnancy test kit, provided by the study to women

who believe they are or might be pregnant. While ideally we would enter women into the study the day they begin using Dot, that is not possible logistically (a woman can download and begin using Dot on any day of her cycle by entering the day her most recent period started). Because she needs to enter the study at the beginning of a cycle (to ensure she is not pregnant prior to entering the study and to obtain a complete history of sexual intercourse throughout the cycle), we will recruit women when they enter their second period start date.

* Rationale and justification for study (i.e. historical background, investigator's personal experience, pertinent medical literature, etc.):

A number of smartphone apps have been developed that help women track their menstrual cycle including Period Tracker, Clue, and Glow. However, most of these are limited to tracking and are not appropriate for pregnancy prevention. Some appear to model cycle lengths with a normal distribution and then estimate the day of ovulation by fixing the luteal phase to be 13 or 14 days, with days around ovulation identified as fertile. There are a number of drawbacks to such an approach. A normal model is sensitive to unusual cycle lengths and may be less accurate when few observations are available. There are problems with fixing the luteal phase as constant. Most important, this approach does not incorporate uncertainty inherent in estimating the day of ovulation.

Some other apps use a symptothermal approach, collecting information about fertility signs (e.g., cervical secretions, basal body temperature, cervix position) and other symptoms (e.g., mood, abdominal pain) and state that they can be used for pregnancy prevention. These include Kindara, Lily, or Groove). While some women are willing to track these variables throughout their cycles and have access to the hardware they sometimes require, others prefer a simpler approach – especially for ongoing pregnancy prevention. Some symptothermal apps are based on proven approaches, but others do not indicate the basis of their claims.

4.

An exception to the issues of unclear or undisclosed algorithms, as well as the input and hardware requirements of some apps, is the CycleBeads® app, based on the Standard Days Method® (SDM) of family planning. SDM is effective for women with self-reported cycles of 26-32 days and flags days 8 through 19 as the days to avoid unprotected intercourse (Arevalo, et al, 2002). The SDM algorithm was derived from calculations of the variability of cycle length, timing of ovulation, and fecundability in relation to ovulation. SDM accounts for these factors while maximizing pregnancy prevention and minimizing the number of flagged days. Results of an efficacy/effectiveness study of SDM indicated a correct use failure rate of <5 and a typical use failure rate of <12 per 100 women/years (Arevalo, et al, 2002). Most SDM users have relied – and continue to rely – on CycleBeads, the physical tool that supports correct provision and use of the method. More recently, to create an additional means to help women understand and use SDM, Cycle Technologies developed the CycleBeads app. Available worldwide to those with access to iPhones and Androids, the app recently has been tested in Kenya, where users reported that it was easy to download and use correctly. Kenya users reported a high rate of continued use (number, citation) over time. Additionally, data from this study found that some women who used the app were new FP users (Ashcroft and Shelus 2016).

However, SDM, and thus the CycleBeads app, has certain limitations. Women eligible to use

the method should have most menstrual cycles between 26 and 32 days long. Regardless of cycle variability or consistent cycle length within that range, 12 days (days 8-19) each cycle are considered fertile. A method that allows shorter or longer cycles and adapts to an individual woman's cycle lengths and variability has the potential to increase access to and use of a fertility awareness method. Dot meets these criteria.

Since its launch in August, 2015, over 130,000 women have downloaded the iPhone version of Dot. Marketing for Dot has been largely limited to a few targeted promotional activities within social media (Facebook) and buzz resulting from media articles (Buzzfeed, Digital Trends, Technically DC). Women's interactions with the app reflect consistency (monthly 37,000 users). Daily, 1,359 users interact with the app with approximately 70% using it for pregnancy prevention, 10% for pregnancy planning and 20% for tracking cycles. Users are interacting with the app for an average of 30.4 seconds, which is enough time for a woman to either read her risk of pregnancy for that day, or enter a new period start date. Across the total number of interactions, 51% are entering a new cycle date. Currently, after four months of use, approximately 15% of women are continuing to use the app. Note, this statistic is very preliminary, as the app has only been available to users for 5 months. Within the context of the proposed study, several efforts, described below and in the Retention Plan, will be implemented to increase retention rates of users.

We will recruit, screen, consent, enroll, admit, and follow-up with women who have downloaded the Android version of the app for the purpose of preventing pregnancy, entered their second period start date, expressed interest in the study, and meet eligibility requirements for using DOT (usual cycle length self-assessed as 20-40 days long with <10 days variation, have not used hormonal contraception for at least 3 months, and, if breastfeeding, have had at least 3 cycles post-partum). They also will meet eligibility requirements for participating in the study, including age (18-39), being sexually active with a male partner, intent to use Dot for at least one year, have (or will install) password or biometric protection on their phone, and subsequently consent to participate in the study.

Data on user behavior will be collected primarily through the Dot app. Women who choose to participate will use Dot via the research module, which is attached to a study-specific version of the app. This version will be functionally identical to the commercially available product, but will include an additional research module to enable data collection. This module will:

- Provide the participant with additional information on the research study,
- Prompt women to enter sexual intercourse data weekly for the prior 7 days,
- Track continued intention to use the app for pregnancy prevention each cycle,
- Allow the study team to track the participants' individual data, and
- Administer a questionnaire after cycles 4, 7, and 10.

Additional demographic data and information about previous family planning use will be collected via a 15-20 minute structured interview conducted over the phone with up to 1200 consenting participants. Data regarding participants' experience with the app and their intention to continue using the app will be collected via phone interview after their first cycle

in the study. An exit interview will be conducted with all participants when they stop using the app (for any reason) or when they complete 13 cycles of Dot use.

Participants also will be given access to a website that will include information about the study, study progress and frequently-asked questions about the study. They will be reminded to seek information about the app in the Frequently-Asked-Questions section of the app itself. In addition, they will receive a token reimbursement for their time in the form of a gift card sent directly to their phones each time they complete a cycle in the study, when they are interviewed after their first cycle in the study, and when they complete their exit interview (regardless of when or why they exit).

Rationale

With advancements in technology, it is possible to implement more sophisticated algorithms while also making information about their fertility easily accessible to women. DOT uses Bayesian statistical methods and utilizes information from various fertility studies to identify potentially fertile days. Using the smartphone app, women only need to record their first day of menses each cycle; DOT flags days with the estimated probabilities of pregnancy above 1-2.25% depending on the number of cycles whose start date she has entered. As more data are collected, DOT appropriately updates these estimates. A prospective study of the efficacy and effectiveness of this approach, as well as an examination of usability, satisfaction, and continuation, are now required.

* Primary objective:

The primary objective of this study is to determine the efficacy/effectiveness of the DOT

5. algorithm under two conditions: 1) correct (or perfect) use, when a woman does not have unprotected intercourse on days identified as fertile; and 2) typical use, when a woman has unprotected intercourse on days identified as fertile.

* Secondary objective:

The secondary objectives of this study are to:

6.
 - Describe the profile of DOT users,
 - Understand how DOT is being used,
 - Understand reasons for discontinuation of DOT,
 - Determine user understanding of DOT messages, and
 - Describe user feedback on using DOT interface and method.

* Inclusion criteria:

Study participants will be recruited from the pool of women who choose to download the app to an Android phone to prevent pregnancy, as determined when they select “prevent pregnancy” as their mode of use.

7.

To be eligible to use the app to prevent pregnancy, women must meet the following criteria:

- Have self-reported usual cycle length between 20 and 40 days with less than 10 days variation in cycle length. The evidence suggests that the fertile days of women with cycle length within this range are more likely to be covered by the identified fertile days. The app

notifies women with cycles outside this range that the method is not appropriate for them.

- Have not used hormonal contraception during their 3 most recent cycles. This gives enough time for fertility and regular cycling to resume.
- Breastfeeding women can be admitted into the study if they meet all other inclusion criteria, delivered at least 6 months ago, and have had at least 3 menstrual cycles post-partum.

To be included in the study, participants will:

- Have downloaded the Android app for pregnancy prevention and indicated that they are interested in participating in the study;
- Meet the DOT eligibility criteria listed above;
- Have provided contact information to learn more about the study or called the call center;
- Be between 18 and 39 at the time of admission. As these are peak years of fertility and menstrual regularity, limiting participants to women in this age group will increase the validity of study results;
- Be potentially at risk of pregnancy (i.e., sexually active with a male partner and not using any form of family planning except condoms or other barrier methods);
- Provide informed consent to participate in the study;
- Have, or be willing to install, a password or biometric protection on their phone to further ensure the confidentiality of data; and
- Live in the U.S.

* Exclusion criteria:

8. Women who do not meet one or more of the inclusion criteria will be excluded from the study.

* Describe the tasks subjects will be asked to perform:

Monitoring intercourse information

The Dot research module will be programmed to provide women with brief weekly questions (which she will receive at approximately 9:00 a.m. or at a time of her choosing) about the days in which they had intercourse during the previous week, and whether it was protected (using a barrier method) or not. Once a woman has submitted her data, she will only be able to edit it by contacting the call center. She will be prompted to approve the final submission prior to completion.

The participant will be able to enter data for up to seven days in the past.

9.
 - If she does not provide this information by 9:00 p.m. on the eighth day, she will receive a message via push notification asking her to complete DOT information for the previous week. If she does not respond, she will receive the same message at 10:00 p.m.
 - For the next 4 days, she will receive a message at 9:00 a.m., followed by messages at 9:00 p.m. and 10:00 p.m., asking her to enter her data for the previous week.
 - o On the fourth day, the message will be complemented with a notification reminding her to complete the data entry activity. If she does not complete it, she will receive a call from an interviewer.
 - On the fifth day the necessary intercourse data is missing, she will receive a message at 9:00 a.m. asking her to enter it. If she doesn't enter the missing data, a call will be placed by the call center staff.

- The interviewer will attempt to reach the woman, up to three times over 3 consecutive days.
 - If the call center reaches her AND the participant is unable to enter or provide the information to the interviewer for the specified dates, the call center will ask the participant if she wants to remain in the study.
 - o If the participant does not want to remain in the study, the call center will conduct the exit interview processes (see below).
 - o If the participant wants to remain in the study, the call center will review her records to determine her retention.
 - ♣ If she has had missing sexual intercourse data for more than three seven-day periods, the interviewer will conduct the exit interview process
- OR
- ♣ If she is missing more than two consecutive weeks of data on days flagged either fertile or non-fertile, the call center will conduct the exit interview process (see below)
 - If after three tries, the call center is unable to reach her, an automated exit questionnaire will be pushed to the participant's phone. This questionnaire will ask:
 1. Why she has not entered data (wants to become pregnant, does not like Dot, wants to use another method, does not want to continue in the study, etc.)
 - ♣ If she responds that she wants to use another method, the participant will be asked which method (with methods listed in check boxes).
 - 2. The participant will receive this questionnaire until she responds for up to three days. If she does not respond after the third day, she will be considered lost to follow up.
 - ♣ If she responds, her responses will be captured and she will be exited from the study.

Monitoring period start-date information

The app routinely tells users when their next period is expected (a range of days). Women participating in the study will receive the standard Dot reminder via push notifications during the expected range of days. The following is a description of the process during each cycle.

- Each time she enters the start date of her period, the participant will receive the "Period Start Date" message, which thanks her for participating in the study and reminds her to call the 800 number or visit the study website if she has any questions.
- If she does not enter her period start date before or during the range of days when Dot calculates that it will start, she receive the "Enter Period Start Date Reminder" for the next 5 days. This reminder asks the participant to please enter her period date as soon as it starts.
- If she has not entered her start date by the 41st day (because DOT is appropriate for women with cycles between 20 and 40 days long), she will receive the "41 Day" message (See Attachment E) inquiring why she has not entered her start date. She will have the options of stating that she thinks she is having a long cycle, stating that she did not enter her period start date because she no longer wants to participate in the study, entering the date her period started, or indicating that she thinks she might be pregnant.

If she thinks she is having a long cycle, she will be exited from the study and be advised (via the routine Dot pop-up shown in Attachment B) that she should use a different method because Dot is not appropriate for her. It will also trigger a pop-up that asks the participant if she is concerned about a possible pregnancy. If the participant responds yes, then the Pregnancy Procedures will be implemented.

If she does not want to continue in the study, she will be exited from the study.

Period Dates:

- If she enters her start date and her cycle was between 20 and 40 days long, she will be continued in the study.
- If the start date she enters indicates a cycle length less than 20 days or more than 40 days, or if it reflects 10 days or more variation in length from her previous cycle(s) in the study, she will be notified that Dot is not appropriate for her based on her cycle length or variability (see routine Dot pop-up in Attachment B), and exited from the study.

Pregnancy Procedures

- If she indicates on the Period Start Date form that she thinks she is pregnant, the call center will be notified, and an interviewer will attempt to reach her (up to five attempts). The interviewer will administer a questionnaire (see Attachment F, Pregnancy Questionnaire), asking whether and how she confirmed her pregnancy and confirming her intercourse history. If she had unprotected intercourse on a day flagged by Dot as fertile, she will be asked if she was aware that was a fertile day.
- The interviewer will remind her that, as was explained to her when she entered the study, we need a photo of her pregnancy test results and that she will receive a home pregnancy test kit (3 tests) via express mail. Prior to recording any address or other personal information, the interviewer will administer a second consent form that is relevant to obtaining the personal information and agreeing to receive the pregnancy test (See attachment in section 12.9). The interviewer will request the best address for mailing the test kit and a name to include on the package. The tests/kits will be sent, along with instructions to 1) use her phone to take and send a photograph of the pregnancy test results (photograph of the completed test) to the interviewer. Note: the camera phone will be activated through an in-app mechanism that will facilitate the photograph and send it without linking the woman's personal information to the photograph. The photograph will be sent directly to the participant file on the interviewer's screen. 2) if the results of the first test are negative or ambiguous, wait 5 days and use the second test. Regardless of test results, she will be encouraged to contact her health care provider for advice. If results are negative, she will be exited from the study and advised to seek another method.

If after five attempts, the call center is unable to reach her, she will receive a questionnaire on her phone asking her why she has not entered data (wants to become pregnant, does not like Dot, wants to use another method, does not want to continue in the study, whether she is using/plans to use another method, and which one). She will receive this questionnaire for up to three days. If she does not respond, she will be considered lost to follow up. If she responds, her responses will be captured and she will be exited from the study.

See the Exit section below for further information about the exit process.

The process related to completing Cycle 1 in the study is different from the above.

When she completes Cycle 1 in the study, she will receive a message via push notification asking her to call the 800 number to speak with an interviewer about her experience using

Dot.

- If she calls, the interviewer will ask her questions regarding her experience with Dot, the opinions about Dot expressed by her partner and others with whom she has discussed it, whether she wants to continue using it to prevent pregnancy, and whether she wants to continue in the study. She also will be asked about her strategies for avoiding unprotected intercourse on fertile days. If she does not want to continue using Dot for pregnancy prevention or if she does not want to continue in the study, she will be exited from the study.
- If she does not call within 24 hours, she will continue to receive this message for another 3 days. If she has not responded, the call center will attempt to contact her (up to three tries) to administer a questionnaire.
- If the call center is unable to reach her after three attempts, she will receive a self-administered questionnaire on her phone asking her about her experience with Dot, what she thinks is her partner's opinion of Dot, whether she has discussed Dot with anyone and if so their opinion about it, and whether she wants to continue to use Dot and participate in the study.
- Some women may not call the number, but continue providing intercourse data. Missing data will be noted, and the woman will continue in the study.
- If she does not respond to the request for an interview or complete the self-administered questionnaire but continues to enter intercourse data, this will be flagged as "missing data" for this participant and she will be considered lost to follow up.

See the Exit section below for further information about the exit process.

Similar procedures will be followed and similar questions asked when she completes cycles 4, 7, and 10. However, for these cycles, she will be asked these questions via a self-administered phone questionnaire instead of an interview.

The 13th cycle completion process is also different from other cycles.

When she completes cycle 13, that is, when she enters the start date of her 14th period in the study, she will receive a pop up alert thanking her for completing the study and requesting that she call the 800 number within the next 24 hours. Alternatively, she can choose to have an interviewer call her by selecting a button. Whether she calls the interviewer or is called by the interviewer, her personal information will not be shared with the interviewer or the call center. This information will be automated and only information relevant to the purpose of the call (study ID number, purpose of interview, relevant interview questions) will appear on the interviewer's computer screen.

If she does not call, the call center will attempt to reach her (up to three attempts). If the interviewer reaches her and she is willing to be interviewed, she will be asked questions about her experience with Dot, her recommendations for any changes to Dot, and her plans to continue using it. If she does not plan to continue using it, she will be asked why (e.g., wants to become pregnant, wants to use another method). If she wants to use another method, she will be asked which one and why she prefers it.

If the call center is not able to reach her after three attempts, she will receive a self-administered questionnaire asking her about her future plans re pregnancy, using Dot, and

using another method.

If she does not respond to either the phone call or the self-administered questionnaire, she will be exited from the study and this will be considered “missing data” for this participant.

* Please indicate who will monitor the study and to whom the monitor will report. Describe the frequency of the monitoring:

IRH

Victoria Jennings (Primary Investigator) as the primary investigator of this study, she will be responsible for all study supervision, monitoring and data analysis. She will ensure that the study receives all ethical approvals from Georgetown University and adheres to those standards throughout the life of this study.

Dominick Shattuck (co-Investigator) will conduct analyses captured through electronic data collection systems and interviews as described in the protocol and ensure that results are reviewed and validated by a secondary, trained statistician. Shattuck, in collaboration with the Research Assistant (TBD) will lead coordination of data tracking, training activities and collaboration between IRH and the entities listed below.

TBD (Research Coordinator) IRH will hire a research coordinator to assist in the daily management of study activities, development of materials for training call center staff, training and monitoring of the call center, facilitation of data checks, and coordination of partner meetings and communication.

10. Lizzy Menstell (Study Coordinator) will support the Research Coordinator in daily management of study activities, and coordination of partner meetings and communication.

Call center

(Key Staff TBD): A specialized health call center will be identified and engaged to administer informed consent, conduct enrollment, conduct phone surveys and serve as a helpline for study participants. The call center will be trained in data collection and research ethics and monitored by IRH.

IRH will lead the training of initial call-center employees and at least one manager at the call center, who can then lead trainings with any additional call center employees who may work on the Dot study. The training will include an overview of the study, research ethics, data security protocols, and each of the data collection components that the call center will be involved in (e.g., consenting, follow-up, exit interviews). Training will include role-play scenarios and practice calls, to assure interviewers understand various potential scenarios.

HITLab:

Frank Fries is the Project Lead for HITLab. He will oversee the development of the research module. He and his team will ensure the functionality of the tool in accordance with the study protocol. During the study, they will continuously monitor and trouble-shoot the research module, respond to queries from IRH, and support other aspects of the study as

needed. They will transfer data to secure servers as described elsewhere in this protocol.

- * Primary Study Endpoint:
11. Final reports will be submitted to the funder in September 2018.
- * Setting in which the study will be conducted:
12. The continental United States
- If this is a multicenter study, please select the type below:
13. National
- * Please provide the estimated local number of subjects (including controls):
14. 1,200
- * Please provide the estimated total number of subjects (including controls):
15. 1,200
- * Please specify how long the study will be open for accrual:
16. Two years and three months, June 2016 to September 2018.
- * Please provide the total study duration, including subject follow-up and data analysis:
17. Data collection: Two years and three months, June 2016 to September 2018. Data analysis: three month, September to December 2018
- * Please provide the estimated duration of the study procedures:
18. Two years six months, June 2016 to December 2018.

10.2 - Information for Protocol Review - Risks

* Does the research involve any of these possible risks or harms to subjects?

1.

Collection of personal or sensitive information in surveys or interviews

* Please describe the nature and degree of risk or harm for the items you selected above:

There is no physical risk to participating in the study. Participants will be drawn from a pool of women who have voluntarily – and completely outside the study – downloaded the Dot app on their phones and begun using as indicated by their having entered their period start date, and have specified that they want to use it for pregnancy prevention. Their risk of pregnancy is associated with their use of Dot rather than by participating in the study. However, there is some risk that participants may feel uncomfortable or embarrassed when discussing certain topics with an interviewer, such as family planning, whether they think they might be pregnant, etc. And they might feel uncomfortable entering data on their phones about having intercourse or using a condom. Additionally, although interviewers will be trained in maintaining confidentiality, there is always some risk that confidentiality will be breached.

* Describe how research-related risks will be minimized.:

Ensuring the security and confidentiality of the research data collect is paramount. Research data entered into the DOT research module will be transmitted and stored in an encrypted fashion and be inaccessible to outside networks. Once data is entered into the module, it will be transmitted over a Transport Layer Security (TLS) encrypted connection to the project's Research Web Portal application.

The Research Web Portal consists of a web application and database. The web application will be the user-facing interface for research participants, call center staff and IRH research

staff. Each will have a separate and role-specific interface. Research participants will have access to study and general information. Call center staff will be able to interact with research participants on an as needed basis. Call center staff will have read only access to specific and limited participant data in order to carry out elements of the research protocol. Authorized IRH research staff will be able to view built-in reports and pull down data sets as necessary.

The research database will be setup on a separate dedicated server and isolated from the public Internet. Data stored on in the research database will be encrypted at the cell level. Direct access to the research database will be restricted to authorized IRH and HITLAB staff.

Access to the Research Web Portal and Dot application transactions will be logged and monitored for unusual activity, unauthorized access attempts and to support compliance requirements (e.g. HIPAA).

IRH will work with the interviewers and managing agency to ensure that they meet ethical compliance (CITI training) and have all necessary documentation. Study training for call center interviewers will include several components associated with qualitative data collection, DOT methodologies, and trouble-shooting the Dot app. Interviewers will be legal U.S. residents with experience conducting these types of interviews, as per the call center where they work. All interviewers will be female.

Study training will include, in addition to the study overview, methodologies and themes, training about conducting research with human subjects and how to deal with situations of stress. Research ethics will be reviewed with the call center staff. The following ethical issues will be emphasized:

- How to follow study procedures to ensure the protection of information collected from participants;
- Qualitative data collection procedures;
- What is meant by confidentiality, privacy and consent (simulated phone interviews will be used to clarify these ethical concepts);
- The voluntary nature of participating in the interviews;
- The importance of assuring participants that they can discontinue the interview without affecting their use of Dot;
- The importance of obtaining and confirming informed consent;
- Referral protocols for issues such as domestic violence, STIs, or other medical matters onto qualified professionals.

Should any adverse event occur, the Principal Investigator will ensure that the adverse event is reported to the IRB in accordance with Georgetown University policy.

Call center data that triggers interaction between interviewers and participants will not reveal personal information. Participants' phone numbers will be stored in the remote database (described above) and linked to the automated dialing system within the call center. Interviewers will not see any participant names, phone numbers or other identifying information (i.e.; email addresses, street addresses, etc.). Information on the interviewer's screen will reveal participant identification number and purpose of the phone call. Additionally, the relevant data collection tools will appear on their screen to guide the

interview.

All data will be entered directly into an information management system and time-stamped. This system will be password protected in the remote server described above. Data within the remote server will be managed by HitLab in compliance with HIPPA and Georgetown University ethical data management standards.

Predetermined data checks will be executed daily within the database programming and aggregate reports sent to the IRH team for review. Additionally, the database will have a de-identified “dashboard” through which the team can run routine data checks on factors including enrollment and retention. HitLab Project Coordinator, Frank Fries, will have access to the full database. More detail is on the data management and coordination can be found in the Data Management Plan.

Study recruitment will only occur for ongoing users of the Dot app who had previously downloaded Dot for personal use and have been using it to prevent pregnancy for at least one menstrual cycle. As a requirement of initially downloading the app for personal use, all users must agree to routine, aggregate collection of their app usage data via Cycle Technologies (see Dot app Privacy Policy). However, all data collected specifically for the research study will be collected independently of the usage data and will not be reported to Cycle Technologies, the mobile carrier or to Android. This will be clarified in the consent process.

As a requirement of initially downloading the app for personal use, all users must agree to routine, aggregate collection of their app usage data via Cycle Technologies. Additionally, app download history may be collected through the mobile carrier and/or Android. However, any and all data collected specifically for the research study will be collected independently, through the app, and will not be reported (or available) to Cycle Technologies, the mobile carrier, or Android.

One inclusion criterion for participation in the study is the mandatory requirement that participants create or use a numeric password specifically to open the app and ensure confidentiality of their data (section 10.0.4). When creating an app password as part of their study onboarding process, participants will be counseled to avoid common passwords (e.g., “1234”) that are easily hacked. Participants will also be reminded, as part of their informed consent process, that although password protecting the app substantially increases their privacy, a minor risk still applies and should be taken into consideration when deciding to participate in this study.

To address this concern, participants will be counseled in both the Informed Consent document and during their study onboarding to complete their data collection in a private location as part of the study onboarding process.

As part of the call center training, IRH will train the call center representatives on how to conduct research calls on sensitive topics (e.g., reproductive/sexual history). Additionally, all call center representatives will complete ethical compliance training (CITI training) prior to

the initiation of the study. Finally, all call center representatives will be female. As part of the informed consent process, participants will be informed that they will be asked to provide information on potentially sensitive issues (such as engagement in sexual intercourse, pregnancy status, etc). Participants who consent to providing this information will be counseled that, in the future, if they find they are uncomfortable answering such study questions, they can choose to skip those questions or withdraw from the study at any point. To address data entry proficiency, all participants will be provided with a short, study onboarding training as part of their initial interview. This interview will provide an overview of how/when to enter research data in the app and who to contact in the event that the participant encounters a problem. All participants will be encouraged to reach out in the event that they have concerns or problems and will be connected to the appropriate contact (Cycle Technologies, study PI, etc).

10.3 - Information for Protocol Review - Data Safety Monitoring Plan

* Please describe how research-related risks to participants will be minimized by using (1) procedures which are consistent with sound research design and which do not unnecessarily expose study participants to risk, (2) whenever appropriate, procedures already being performed on the study participants, and (3) other. Such procedures might include tests that monitor for toxicity, close monitoring procedures, etc.:

Ensuring the security and confidentiality of the research data collected is paramount. Research data entered into the DOT research module will be transmitted and stored in an encrypted fashion and be inaccessible to outside networks. Once data is entered into the module, it will be transmitted over a Transport Layer Security (TLS) encrypted connection to the project's Research Web Portal application.

The Research Web Portal consists of a web application and database. The web application will be the user-facing interface for research participants, call center staff and IRH research staff. Each will have a separate and role-specific interface. Research participants will have access to study and general information. Call center staff will be able to interact with research participants on an as needed basis. Call center staff will have read only access to specific and limited participant data in order to carry out elements of the research protocol. Authorized IRH research staff will be able to view built-in reports and pull down data sets as necessary.

The research database will be setup on a separate dedicated server and isolated from the public Internet. Data stored on in the research database will be encrypted at the cell level. Direct access to the research database will be restricted to authorized IRH and HITLAB staff.

Access to the Research Web Portal and Dot application transactions will be logged and monitored for unusual activity, unauthorized access attempts and to support compliance requirements (e.g. HIPAA).

IRH will work with the interviewers and managing agency to ensure that they meet ethical compliance (CITI training) and have all necessary documentation. Study training for call center interviewers will include several components associated with qualitative data collection, DOT methodologies, and trouble-shooting the Dot app. Interviewers will be legal

U.S. residents with experience conducting these types of interviews, as per the call center where they work. All interviewers will be female.

Study training will include, in addition to the study overview, methodologies and themes, training about conducting research with human subjects and how to deal with situations of stress. Research ethics will be reviewed with the call center staff. The following ethical issues will be emphasized:

- How to follow study procedures to ensure the protection of information collected from participants;
- Qualitative data collection procedures;
- What is meant by confidentiality, privacy and consent (simulated phone interviews will be used to clarify these ethical concepts);
- The voluntary nature of participating in the interviews;
- The importance of assuring participants that they can discontinue the interview without affecting their use of Dot;
- The importance of obtaining and confirming informed consent;
- Referral protocols for issues such as domestic violence, STIs, or other medical matters onto qualified professionals.

Should any adverse event occur, the Principal Investigator will ensure that the adverse event is reported to the IRB in accordance with Georgetown University policy.

Call center data that triggers interaction between interviewers and participants will not reveal personal information. Participants' phone numbers will be stored in the remote database (described above) and linked to the automated dialing system within the call center. Interviewers will not see any participant names, phone numbers or other identifying information (i.e.; email addresses, street addresses, etc.). Information on the interviewer's screen will reveal participant identification number and purpose of the phone call. Additionally, the relevant data collection tools will appear on their screen to guide the interview.

All data will be entered directly into an information management system and time-stamped. This system will be password protected in the remote server described above. Data within the remote server will be managed by HitLab in compliance with HIPPA and Georgetown University ethical data management standards.

Predetermined data checks will be executed daily within the database programming and aggregate reports sent to the IRH team for review. Additionally, the database will have a de-identified "dashboard" through which the team can run routine data checks on factors including enrollment and retention. HitLab Project Coordinator, Frank Fries, will have access to the full database. More detail is on the data management and coordination can be found in the Data Management Plan.

Study recruitment will only occur for ongoing users of the Dot app who had previously downloaded Dot for personal use and have been using it to prevent pregnancy for at least one

menstrual cycle. As a requirement of initially downloading the app for personal use, all users must agree to routine, aggregate collection of their app usage data via Cycle Technologies (see Dot app Privacy Policy). However, all data collected specifically for the research study will be collected independently of the usage data and will not be reported to Cycle Technologies, the mobile carrier or to Android. This will be clarified in the consent process.

As a requirement of initially downloading the app for personal use, all users must agree to routine, aggregate collection of their app usage data via Cycle Technologies. Additionally, app download history may be collected through the mobile carrier and/or Android. However, any and all data collected specifically for the research study will be collected independently, through the app, and will not be reported (or available) to Cycle Technologies, the mobile carrier, or Android.

One inclusion criterion for participation in the study is the mandatory requirement that participants create or use a numeric password specifically to open the app and ensure confidentiality of their data (section 10.0.4). When creating an app password as part of their study onboarding process, participants will be counseled to avoid common passwords (e.g., "1234") that are easily hacked. Participants will also be reminded, as part of their informed consent process, that although password protecting the app substantially increases their privacy, a minor risk still applies and should be taken into consideration when deciding to participate in this study.

To address this concern, participants will be counseled in both the Informed Consent document and during their study onboarding to complete their data collection in a private location as part of the study onboarding process.

As part of the call center training, IRH will train the call center representatives on how to conduct research calls on sensitive topics (e.g., reproductive/sexual history). Additionally, all call center representatives will complete ethical compliance training (CITI training) prior to the initiation of the study. Finally, all call center representatives will be female.

As part of the informed consent process, participants will be informed that they will be asked to provide information on potentially sensitive issues (such as engagement in sexual intercourse, pregnancy status, etc). Participants who consent to providing this information will be counseled that, in the future, if they find they are uncomfortable answering such study questions, they can choose to skip those questions or withdraw from the study at any point. To address data entry proficiency, all participants will be provided with a short, study onboarding training as part of their initial interview. This interview will provide an overview of how/when to enter research data in the app and who to contact in the event that the participant encounters a problem. All participants will be encouraged to reach out in the event that they have concerns or problems and will be connected to the appropriate contact (Cycle Technologies, study PI, etc).

2. * Please describe what action(s) will be taken if any of the Adverse Events listed in the "Risks" section occur:

The study call center will document the adverse event and will notify the study PI immediately in the case of any adverse events. The study PI will notify the Georgetown University IRB.

* Please describe how risks to participants are reasonable in relation to anticipated benefits:

There are no physical risks to participating in the study. The only possible risks are that women may feel uncomfortable providing data about their menstruation or sexual activity.

3. Women participating in the study will not benefit directly from their participation other than receiving a token reimbursement for their time. However, they will be aware that they are contributing to the understanding and potential improvement of a family planning method that is available to women worldwide.

* Will there be a Data Safety Monitoring Board/Committee to review this study?

☐ Yes ☒ No

4. [A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. Patients will be told about new information from this or other studies that may affect their health, welfare, or willingness to stay in this study.]

5. If there is no DSMB/DSMC, please specify who will be responsible for monitoring the study:
The study PI is responsible for monitoring the study.

* Please describe plans for interim analysis, monitoring the study, and the safety of participants:

- No interim analyses are planned for the survey data. Data will be screened periodically by the study team to identify issues related to discontinuation. Any adverse events will be recorded immediately by study staff and reported to the study PI, then to the IRB.

The only adverse event anticipated is pregnancy. Pregnancy procedures are described in the study documentation.

7. * Please describe plans for ensuring compliance with requirements regarding the reporting of adverse events, including plans for reporting of adverse events to the IRB, sponsor, and/or regulatory agencies:

The study PI will notify the Georgetown University IRB.

* Please describe plans for retaining subjects and ensuring follow-up visits and tests:

Follow-up will focus on two primary pieces of information: Intercourse and Period Start Date. Additionally, we have a retention plan described in the study documentation as an attachment.

Monitoring intercourse information

8. The Dot research module will be programmed to provide women with brief weekly questions (which she will receive at approximately 9:00 a.m. or at a time of her choosing) about the number of times they had intercourse during the previous week, and whether it was protected (using a barrier method) or not. Once a woman has submitted her data, she will only be able to edit it by contacting the call center. She will be prompted to approve the final submission prior to completion. Her data will initially be stored locally on her phone, and transmitted to the data set as soon as the participant has a wifi or cellular connection. Once transmitted, the data will be deleted from her phone. Intercourse data for all days when she marked as having intercourse will be required in order for the woman to exit the data collection procedure.

The participant will be able to enter data for up to seven days in the past.

- If she does not provide this information by 9:00 p.m. on the eighth day, she will receive a message via push notification asking her to complete DOT information for the previous week. If she does not respond, she will receive the same message at 10:00 p.m.
 - For the next 4 days, she will receive a message at 9:00 a.m., followed by messages at 9:00 p.m. and 10:00 p.m., asking her to enter her data for the previous week”.
 - o On the fourth day, the message will be complemented with a notification reminding her to complete the data entry activity. If she does not complete it, she will receive a call from an interviewer.
 - On the fifth day the necessary intercourse data is missing, she will receive a message at 9:00 a.m. asking her to enter it. If she doesn't enter the missing data, a call will be placed by the call center staff.
 - The interviewer will attempt to reach the woman, up to three times over 3 consecutive days.
 - If the call center reaches her AND the participant is unable to enter or provide the information to the interviewer for the specified dates, the call center will ask the participant if she wants to remain in the study.
 - o If the participant does not want to remain in the study, the call center will conduct the exit interview processes (see below).
 - o If the participant wants to remain in the study, the call center will review her records to determine her retention.
 - ♣ If she has had missing sexual intercourse data for more than three seven-day periods, the interviewer will conduct the exit interview process
- OR
- ♣ If she is missing more than two consecutive weeks of data on days flagged either fertile or non-fertile, the call center will conduct the exit interview process (see below)
 - If after three tries, the call center is unable to reach her, an automated exit questionnaire will be pushed to the participant's phone. This questionnaire will ask:
 1. Why she has not entered data (wants to become pregnant, does not like Dot, wants to use another method, does not want to continue in the study, etc.)
 - ♣ If she responds that she wants to use another method, the participant will be asked which method (with methods listed in check boxes).
 - 2. The participant will receive this questionnaire until she responds for up to three days. If she does not respond after the third day, she will be considered lost to follow up.
 - ♣ If she responds, her responses will be captured and she will be exited from the study.

Monitoring period start-date information

The app routinely tells users when their next period is expected (a range of days). Women participating in the study will receive the standard Dot reminder via push notifications during the expected range of days. The following is a description of the process during each cycle.

- Each time she enters the start date of her period, the participant will receive the “Period Start Date” message, which thanks her for participating in the study and reminds her to call the 800 number or visit the study website if she has any questions.

- If she does not enter her period start date before or during the range of days when Dot calculates that it will start, she will receive the “Enter Period Start Date Reminder” for the next 5 days. This reminder asks the participant to please enter her period date as soon as it starts.
- If she has not entered her start date by the 41st day (because DOT is appropriate for women with cycles between 20 and 40 days long), she will receive the “41 Day” message (See Attachment E) inquiring why she has not entered her start date. She will have the options of stating that she thinks she is having a long cycle, stating that she did not enter her period start date because she no longer wants to participate in the study, entering the date her period started, or indicating that she thinks she might be pregnant.

If she thinks she is having a long cycle, she will be exited from the study and be advised (via the routine Dot pop-up shown in Attachment B) that she should use a different method because Dot is not appropriate for her. It will also trigger a pop-up that asks the participant if she is concerned about a possible pregnancy. If the participant responds yes, then the Pregnancy Procedures (Attachment L) will be implemented.

If she does not want to continue in the study, she will be exited from the study.

Period Dates:

- If she enters her start date and her cycle was between 20 and 40 days long, she will be continued in the study.
- If the start date she enters indicates a cycle length less than 20 days or more than 40 days, or if it reflects 10 days or more variation in length from her previous cycle(s) in the study, she will be notified that Dot is not appropriate for her based on her cycle length or variability (see routine Dot pop-up in Attachment B), and exited from the study.

Pregnancy Procedures

- If she indicates on the Period Start Date form that she thinks she is pregnant, the call center will be notified, and an interviewer will attempt to reach her (up to five attempts). The interviewer will administer a questionnaire (see Attachment F, Pregnancy Questionnaire), asking whether and how she confirmed her pregnancy and confirming her intercourse history. If she had unprotected intercourse on a day flagged by Dot as fertile, she will be asked if she was aware that was a fertile day.
- The interviewer will remind her that, as was explained to her when she entered the study, we need a photo of her pregnancy test results and that she will receive a home pregnancy test kit (3 tests) via express mail. The interviewer will request the best address for mailing the test kit and a name to include on the package. The tests/kits will be sent, along with instructions to 1) use her phone to take and send a photograph of the pregnancy test results (photograph of the completed test) to the interviewer. Note: the camera phone will be activated through an in-app mechanism that will facilitate the photograph and send it without linking the woman’s personal information to the photograph. The photograph will be sent directly to the participant file on the interviewer’s screen. 2) if the results of the first test are negative or ambiguous, wait 5 days and use the second test. Regardless of test results, she will be encouraged to contact her health care provider for advice. If results are negative, she will be exited from the

study and advised to seek another method.

If after five attempts, the call center is unable to reach her, she will receive a questionnaire on her phone asking her why she has not entered data (wants to become pregnant, does not like Dot, wants to use another method, does not want to continue in the study, whether she is using/plans to use another method, and which one). She will receive this questionnaire for up to three days. If she does not respond, she will be considered lost to follow up. If she responds, her responses will be captured and she will be exited from the study.

See the Exit section below for further information about the exit process.

The process related to completing Cycle 1 in the study is different from the above.

When she completes Cycle 1 in the study, she will receive a message via push notification asking her to call the 800 number to speak with an interviewer about her experience using Dot.

- If she calls, the interviewer will ask her questions regarding her experience with Dot, the opinions about Dot expressed by her partner and others with whom she has discussed it, whether she wants to continue using it to prevent pregnancy, and whether she wants to continue in the study. She also will be asked about her strategies for avoiding unprotected intercourse on fertile days. If she does not want to continue using Dot for pregnancy prevention or if she does not want to continue in the study, she will be exited from the study.

- If she does not call within 24 hours, she will continue to receive this message for another 3 days. If she has not responded, the call center will attempt to contact her (up to three tries) to administer a questionnaire.

- If the call center is unable to reach her after three attempts, she will receive a self-administered questionnaire on her phone asking her about her experience with Dot, what she thinks is her partner's opinion of Dot, whether she has discussed Dot with anyone and if so their opinion about it, and whether she wants to continue to use Dot and participate in the study.

- Some women may not call the number, but continue providing intercourse data. Missing data will be noted, and the woman will continue in the study.

- If she does not respond to the request for an interview or complete the self-administered questionnaire but continues to enter intercourse data, this will be flagged as "missing data" for this participant and she will be considered lost to follow up.

See the Exit section below for further information about the exit process.

Similar procedures will be followed and similar questions asked when she completes cycles 4, 7, and 10. However, for these cycles, she will be asked these questions via a self-administered phone questionnaire instead of an interview.

The 13th cycle completion process is also different from other cycles.

When she completes cycle 13, that is, when she enters the start date of her 14th period in the study, she will receive a pop up alert thanking her for completing the study and requesting that

she call the 800 number within the next 24 hours. Alternatively, she can choose to have an interviewer call her by selecting a button. Whether she calls the interviewer or is called by the interviewer, her personal information will not be shared with the interviewer or the call center. This information will be automated and only information relevant to the purpose of the call (study ID number, purpose of interview, relevant interview questions) will appear on the interviewer's computer screen.

If she does not call, the call center will attempt to reach her (up to three attempts). If the interviewer reaches her and she is willing to be interviewed, she will be asked questions about her experience with Dot, her recommendations for any changes to Dot, and her plans to continue using it. If she does not plan to continue using it, she will be asked why (e.g., wants to become pregnant, wants to use another method). If she wants to use another method, she will be asked which one and why she prefers it.

If the call center is not able to reach her after three attempts, she will receive a self-administered questionnaire asking her about her future plans re pregnancy, using Dot, and using another method.

If she does not respond to either the phone call or the self-administered questionnaire, she will be exited from the study and this will be considered "missing data" for this participant.

9. * Please describe the risk categorization for your protocol:
Minimal Risk

10.5 - Information for Protocol Review [Unanticipated Problems and Procedures for Minimizing Risks]

- * Who is the individual primarily responsible for reporting unanticipated problems to the
1. IRB (Name and Position):

Victoria Jennings, Study PI

* Please describe what will happen to the already collected data if subjects may decide to withdraw/dropout before study completion. Include examples of reasons that may prompt subject withdrawal/dropout.

Note: Please describe partial withdrawal and its implications in the Informed Consent Document as well.

2. Data will be recorded and included in the analysis. This study is centered on a mobile phone app. Research in mobile technologies reflects a high rate of discontinuation. If we recruit the upper threshold of our sample size, we could see discontinuation rates around 80%. This is, in part, because we are looking to retain 250 women for a maximum of 13 menstrual cycles, providing us with the power to test contraceptive efficacy. We understand and anticipate some women will drop, because mobile app retention for more than 6-8 months, in general, is extremely low.

Some women will discontinue from the study due to pregnancy. This is articulated in the documentation and study procedures.

* Please describe potential benefits, if any, to study participants and/or society as a whole. Include only those benefits that may result from the research. Compensation is not considered a benefit.

If there are no benefits to subjects, please state so explicitly.

3. There are no benefits to study participants. However, benefits to society as a whole include: 1) the availability of an easily accessible, low cost method of family planning that meets the needs of many women/couples worldwide (pending study results); and 2) because the use of mobile phones for family planning is novel, and women's ability to understand and use the app is unknown, the study will provide evidence of usability and assess acceptability of a mobile phone app to support use of this family planning method based on fertility awareness.

- * Please describe the alternatives to participation in this study. If the only alternative is not participating (for example: survey research, observational study), please state so:
4. The alternative to participation in the study is not participating in the study.

11.0 - Recruitment Techniques

*

All recruitment materials must have IRB approval and be **attached to this application in Section 14.**

1. Please indicate all techniques that apply:

Recruitment Technique

Other

11.1 - Recruitment Techniques - Other

* Please describe the "other" recruitment techniques:

Participants will be recruited into the study using a pop-up in the Dot app, described below.

1. Upon entering their second period start date, a pop-up alerts users that we are conducting a study to learn about how well DOT helps women prevent pregnancy over time and how it can be improved. The alert will provide a link to a website if they want to learn more about the study. The alert will ask if they would like to learn more and include three choices: "Yes", "Ask me later", and "No, don't ask me again". If the woman clicks "yes", she will be asked to answer 6 pre-screening questions that include: her age, desire to avoid pregnancy for at least one year, current sexual relationship, typical cycle length, recent hormonal method use, and desire to be contacted by an interviewer. Women will also be provided a phone number and the option to call and interviewer for recruitment.

Women who want to be asked later will receive the opening message following their entry of period start dates up to two more times. After the third time, they will not receive the message again.

Those who respond that they are not interested will not be contacted again.

Advertisements:

Although women may view advertisements for the Dot app, the only information they will receive about the study will come through a push notification asking if they are interested in participating in a study.

Participants have two options for an initial study screening; either they can call the call center directly, or they can schedule a time to be contacted by a call center representative. In both circumstances, the call center representative will thank her for her interest in the study and review the screening/eligibility questions with her (See attachment B). If she is eligible, the interviewer will then continue with the informed consent process (See attachment C).

11.6 - Selection of Subjects

* Please enter the age range of the subjects:

1. 18-39

* Please select the gender of subjects (select all that apply):

2.

Female

* Please describe your source of subjects:

Recruitment and enrollment will be determined in a multiphase process for women who are current Dot users, elect to participate in the research, meet pre-screening criteria, meet screening criteria through a phone interview, and consent to participate.

The population of eligible participants for this study is women who 1) have begun using Dot for pregnancy prevention; 2) entered their second period start date (i.e., have completed one cycle – in whole or in part – of Dot use), and 3) have indicated that their first cycle was 20-40 days long. Waiting for the second period date ensures that women are not pregnant at the time of study enrollment and allows time to recruit the woman and enroll her into the study before her pregnancy status for that cycle is compromised. Enrolling them when they enter their second period start date allows us to capture a complete sexual history from the initiation of that cycle moving forward. Having had a first cycle between 20 and 40 days suggests that they 3. are eligible to use Dot. They will be recruited into the study using a pop-up, described below.

Upon entering their second period start date, a pop-up alerts users that we are conducting a study to learn about how well DOT helps women prevent pregnancy over time and how it can be improved. The alert will provide a link to a website if they want to learn more about the study. The alert will ask if they would like to learn more and include three choices: “Yes”, “Ask me later”, and “No, don’t ask me again”. If the woman clicks “yes”, she will be asked to answer 6 pre-screening questions that include: her age, desire to avoid pregnancy for at least one year, current sexual relationship, typical cycle length, recent hormonal method use, and desire to be contacted by an interviewer. Women will also be provided a phone number and the option to call and interviewer for recruitment.

Women who want to be asked later will receive the opening message up to two more times. After the third time, they will not receive the message again.

Those who respond that they are not interested will not be contacted again.

11.7 - Safeguards for Special Populations

* Please select the special populations involved in the study, if any, and describe what additional safeguards will be in place to protect these populations from coercion or undue influence to participate:

	Special Population	Safeguards
1.	View Pregnant Women, Fetuses and Neonates	We are not recruiting pregnant women into this study. This is a study of a fertility awareness family planning method, thus we anticipate some women (less than 30) may become pregnant. Women who do get pregnant will not continue in the research study and be referred to seek medical care. Information about the study goals and expectations are clear in the consent form and women can choose to use alternative family planning methods if they so choose. Information about other family planning methods and the risks entailed in using Dot are present within the Apps FAQs, the participant website and consent form.